## REMARKS

Claims 58, 62, 64, 66, 69, 72, 76, 79, 81, 84, 86, 89, 92, 95, and 98 having been amended, the pending claims are claims 58-102.

The amendment of claims 58, 62, 64, 66 and 69 to delete recitation of "an EphA2 agonist" and substitute therefor "a compound that increases the phosphotyrosine content of EphA2," and analogous amendments made to claims 72, 76, 79, 81, 84, 86, 89 92, 95 and 98 are supported, for example, by the specification at page 3, lines 1-6. For reasons set forth below, it is respectfully submitted that these amendments are not narrowing amendments.

The specification has been amended at page 5, line 11; page 7, line 4; page 11, line 9; page 12, line 32; and page 18, lines 9-10 and line 15; to correct obvious typographical errors. The specification is further amended at page 6, line 13, to recite identifying information for the biological deposits of murine hybridomas B2D6 and D7. The specification is further amended at page 8, line 31, to clarify that the in vitro experiments performed in Example 1 were conducted using B2D6 antibody. This amendment is supported by the specification at, for example, page 9, line 29.

### Election/Restriction/Action Following Election

In response to the Restriction Requirement mailed 6 May 2002, Applicants elected, with traverse, the invention of group II, and further elected breast cancer in compliance with the species election requirement. The Examiner stated as a result of Applicant's election, claims 58-102 were examined on the merits "as they are drawn to a method of treating breast cancer as the elected species." Applicants respectfully submit that the examination was, as a result, incomplete.

MPEP 809.02(c) specifically states that an Examiner's action subsequent to an election of species should include a *complete action* on the merits *of all claims readable on the elected species*. All pending claims (claims 58-102) read on the elected species (breast cancer); all are generic. Indeed, the species "breast cancer" is only recited in claims 101 and 102, and then as a

member of Markush group. Thus, MPEP 809.02(c) requires that the Examiner render a *complete action* on the merits of all pending claims 58-102.

The species election, if required by an Examiner, is made to ease the search burden on the Examiner. If a search of the species reveals no prior art, it is respectfully submitted that the Examiner is obligated to consider the full scope of any generic claims.

Applicants contend that, in view of the failure of the search to turn up any invalidating breast cancer art, the Office Action was incomplete in that the scope of the examination of claims 58-102 was nonetheless limited by the species election. It is respectfully submitted that the Applicants are entitled to an examination of the pending claims according to their full scope, namely, a method for treating metastatic cancers.

Accordingly, if the Examiner finds that any of the claims are still not allowable, Applicants respectfully request a second nonfinal action directed to the full scope of the pending claims.

## Request to Correct Inventorship

A Request to Correct Inventorship under 37 C.F.R. §1.48(b) is submitted herewith. As noted in the Applicants' Response to the Restriction Requirement, the election of the invention of group II and the cancellation of the remaining claims necessitates a change in inventorship in that Katherine E. Kilpatrick is not an inventor of the pending claims. Amendment of the above-identified patent application to delete Katherine E. Kilpatrick as inventor is respectfully requested.

## Information Disclosure Statements Mailed February 14, 2001, March 13, 2001, September 11, 2001 and December 27, 2001

The Examiner indicated that the documents submitted with the Information Disclosure Statement (IDS) filed on February 14, 2001, cannot be located. However, in a telephone message left with Applicants' Representative Victoria Sandberg on Feb. 7, 2003, the Examiner indicated that the documents have subsequently been found. Applicants thank the Examiner for

the effort expended in locating these documents, and request consideration of the Information Disclosure Statement filed February14, 2001.

Applicants note also that the Office Action Summary indicates that three IDS documents (paper nos. 6,10 and 12) were supposed to have been attached but were not received by Applicants' Representatives. We assume these represented IDS's filed on March 13, 2001, September 11, 2001 and December 27, 2001. The Examiner is kindly requested to provide a copy of the initialed 1449s with the next official communication.

Specification

The Examiner objects to the specification on the grounds that essential material is improperly incorporated by reference. The Examiner states that how to make the EphA2 agonist Ephrin-A1-Fc is essential to practice the instantly claimed invention, and objects to the incorporation by reference of Miao et al. for this purpose.

This objection is respectfully traversed. "Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode. As is discussed in more detail below, it is submitted that the invention, as presently claimed, is adequately described in and enabled by the specification. With respect to the allegedly improper incorporation by reference of Miao et al., Applicants note that Ephrin A1-Fc is readily available commercially. For example, the product can be ordered from Sigma-Aldrich Chemical Company under the product number E9902 (see attached printout from the company website, cited in the Supplemental Information Disclosure submitted herewith). Applicants therefore submit that amendment of the specification to incorporate the teachings of Maio et al. is not required.

Reconsideration and withdrawal of the objection to the specification is respectfully requested.

Rejection under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 58-102 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. This rejection is respectfully traversed.

Specifically, claims 58-71 and 101 were rejected because the metes and bounds of the term "an EphA2 agonist" are allegedly not clear. Claims 72-100, and 102 were rejected as well because the metes and bounds of the term "EphA2 agonistic antibody" are allegedly not clear. Applicants disagree, and maintain that this term is adequately defined in the specification, for example at page 3, lines 1-9. Nevertheless, for clarification only and to advance prosecution of the above-identified application, claims 58, 62, 64, 66 and 69 are amended to delete recitation of "an EphA2 agonist" and substitute therefor "a compound that increases the phosphotyrosine content of EphA2." Likewise, claims 72, 79, 89 and 95 are amended to delete recitation of "an agonistic antibody" and substitute therefore "an anti-EphA2 antibody that increases the phosphotyrosine content of EphA2." Analogous amendments are made to claims 76, 81, 84, 86, 92 and 98. Applicants note that this clarification is consistent with the Examiner's assumption that an EphA2 agonist is a compound that restores the function of EphA2 receptor by increasing the phosphotyrosine content of the EphA2 receptor, and an EphA2 agonistic antibody is an antibody that restores tyrosine phosphorylation of the EphA2 receptor. For this and other reasons, Applicants further submit that amending the claims to recite "an anti-EphA2 antibody that increases the phosphotyrosine content of EphA2" does not constitute a narrowing amendment.

Reconsideration and withdrawal of the rejection of claims 58-102 under 35 U.S.C. §112, second paragraph, is respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 58-102 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the relevant art that the inventors, at the time the application was filed, *had possession* of the claimed invention (emphasis in the original). This rejection is respectfully traversed.

The Examiner characterizes claims 58-71 and 101 as being drawn to a method of cancer treatment using a "genus of products claimed as EphA2 agonist." Likewise, the Examiner characterizes claims 72-100 and 102 as being drawn to a method of metastatic cancer treatment using a "genus of products claimed as EphA2 agonistic antibody." The Examiner further states that since the genus includes a large number of unpredictable species, possession of only one species is not seen as sufficient to reasonably convey possession of the entire genus.

Applicants disagree. It is respectfully submitted that it is not necessary to be able to predict in advance exactly *which* compounds increase the phosphotyrosine content of EphA2. Applicants have made a very important contribution to the development of cancer therapeutics by characterizing the relationship between EphA2 and cancer, and more particularly by recognizing that activating EphA2 in cancer cells by *increasing its phosphotyrosine content* has therapeutic benefit. The skill in the relevant art is very high, and the identification of particular compounds and methods for increasing the phosphotyrosine content of EphA2 are well within the skill of the relevant art workers, particularly in view of the teachings of the present specification. The examples describe a convenient assay for evaluating the phosphotyrosine content of EphA2, thereby providing a straightforward way to identify compounds that increase the phosphotyrosine content of EphA2. The Examiner's attention is directed to the specification at page 16, lines 8-14:

> To measure EphA2 stimulation, the phosphotyrosine content of immunoprecipitated EphA2 was measured by Western blot analysis with phosphotyrosine specific antibodies. Whereas the EphA2 in vector-transfected MCF-10 cells was tyrosine phosphorylated, EphA2 was not tyrosine phosphorylated in $MCF^{EphA2}$ cells. The decreased phosphotyrosine content was confirmed using multiple EphA2 antibodies for immunoprecipitation (D7, B2D6) and different phosphotyrosine-specific antibodies (4G10, PY20) for Western blot analyses.

Applicants have taught everything necessary to perform the invention as claimed. It is not a difficult matter, in view of the Applicants' teachings, for a skilled artworker to quickly identify or develop many varied compounds that increase the phosphotyrosine content of EphA2 in cancer cells. To limit the Applicant to a particular exemplary compound that increases the phosphotyrosine content of EphA2, or to a particular exemplary method of increasing phosphotyrosine content, would unfairly deprive Applicants of the protection to which they are entitled as a result of their important discovery, allowing others to reap an unjust benefit. The claimed process involves increasing the phosphotyrosine content of EphA2 in the cancer cell. Having clearly identified an assay for measuring an increase in phosphotyrosine content of EphA2, the Applicants have established possession of the claimed method as required by 35 U.S.C. §112, first paragraph.

The Examiner is reminded that Written Description Guidelines and MPEP 2163 both recognize that there may be situations where the description of only one species adequately supports a genus. Applicants submit that in this application falls into that category. Note only does the specification set forth the novel and unexpected connection between increased phosphotyrosine content (stimulation) of EphA2 and an abatement of metastatic activity (including an assay for phosphotyrosine content), but it also describes "protein, protein inhibitors, antisense oligonucleotides, or small molecule inhibitors" (page 3, lines 11-12), "monoclonal antibodies, polyclonal, artificial and hybrid antibodies" (page 3, lines 12-13) and "natural or artificial ligands, peptides, anti-sense, ATP analogs or other small molecules" capable of specifically targeting EphA2. After reading the specification and in combination with knowledge of the art, one of skill in the art can immediately comprehend the many options for increasing the phosphotyrosine content of EphA2. The specification contains a description of relevant identifying characteristics *of the method* sufficient to allow a person skilled in the art to recognize that the inventor had possession of the claimed invention.

The Examiner further rejected claims 58-102 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to *enable* one skilled in the art to which pertains, or with which it is most nearly connected, to *make and/or use* the invention (emphasis in the original). This rejection is respectfully traversed.

In characterizing the claims, the Examiner states that claims 58-65, 72-88, 101 and 102 are drawn to a method of breast cancer treatment by administering a therapeutically effective amount of EphA2 agonist and EphA2 antibodies. The Examiner states that these claims, as well as claims 68, 71, 91, and 97 are drawn to a method of cancer treatment using either EphA2 agonist and EphA2 agonistic antibody. The Examiner also states claims 66, 67, 89, 90, 92-94 are drawn to a method of reducing the invasiveness of a metastatic cancer cell using either EphA2 agonist or EphA2 agonistic antibody, and claims 69, 79, 95, 96, 98-102 are drawn to method for reducing the proliferative behavior of a metastatic cancer cell using either EphA2 agonist or EphA2 agonistic antibody. The Examiner further states that the claims as written are interpreted as cancer treatment method (with the elected species of breast cancer) using either EphA2 agonist or EphA2 agonistic antibody.

At the outset, Applicants take issue with the Examiner's statement that these claims are drawn to a method of breast cancer treatment. These claims are drawn to a general method of cancer treatment, not specifically breast cancer treatment. It is respectfully submitted that the species election is neither relevant nor operative to an analysis of *enablement* of a generic claim. Even if it were, since no art rejections were made on the basis of the breast cancer species, it is respectfully submitted that the generic claim must be examined to the extent of its full scope.

The specification teaches, for example, an EphA2 agonist (EphrinA1-Fc, the peptide ligand conjugate) that increased the phosphotyrosine content in EphA2-overexpressing breast cancer cells in culture, reduced colony formation and restored a spherical phenotype to the cells (Example 8, page 18, lines 7-16).

As noted above, the specification clearly sets forth (1) a connection between phosphotyrosine content and EphA2 activity; (2) a method for evaluating changes in phosphotyrosine content of EphA2 in a cancer cell; (3) a wide variety of examples of agents

(candidate agonists) that can be readily assayed for their effect on phosphotyrosine activity and (4) the use of agonists in a therapeutic context to alter the expression of EphA2 (e.g., specification at page 3, lines 9-10).

The Examiner's main concern appears to be the lack of *in vivo* data in the specification. However, proposed *in vivo* experiments were described in detail (see e.g., the specification at page 12, line 31, through page 14, line 14; see also page 16, line 19 through page 17, line 33), along with expected results. In addition, Applicants draw the Examiner's attention to the experiment reported in Example 8 at page 18. Although this is an "*in vitro*" experiment (cell culture), Matrigel is a three-dimensional culture system that much more closely approximates the natural environment of cells than two-dimensional cultures. The correlation between cell behavior in Matrigel and cell behavior in their natural environment is therefore thought to be superior to other in vitro systems.

Still in vitro

Additionally, *in vivo* experiments have now been carried out, and they unequivocally support the teachings of the specification. Applicants believe the pending claims are fully enabled, but can provide *in vivo* data by way of declaration if such evidence would assist in supporting the patentability of the claims.

The Examiner further states that the specification does provide enablement for the claims drawn to the method of using the EphA2 agonistic antibody because the specification does not teach how to make the broad range of EphA2 agonistic antibody that could be used in the claimed invention.

Applicants disagree. Methods of making hybridomas are well known in the art (specification at page 6, lines 14-17). In addition, a particular method, using the RIMMS strategy, is detailed in the specification (page 5, line 24, bridging to page 6, line 13). Notably, of the first four hybridomas to be characterized, two recognized independent epitopes on EphA2 (specification at page 6, lines 8-9). Screening hybridomas to identify an antibody that binds to a protein of interest is also well known in the art (see, e.g., *In re Wands*, 8 U.S.P.Q.2d, 1400, Fed. Cir. 1988). In addition, a particular screening method to identify which of the hybridomas produce antibodies that bind to EphA2 is described in Example 5 at page 14, line 16, bridging to

page 15, line 7. Finally, the specification sets forth methods for evaluating whether the antibodies increase the phosphotyrosine content of EphA2 (e.g., Example 6 at page 16, lines 9-14) or reduce the invasiveness of the metastatic cancer (e.g., Example 4 at page 12, line 28, bridging to page 14, line 14).

Finally, Applicants wish to bring to the Examiner's attention that hybridoma cell line B2D6 was deposited with the American Type Culture Collection on December 8, 2000, and assigned accession number PTA-2754, thereby satisfying the enablement requirements of 35 U.S.C. §112, first paragraph. The Statement of Availability and the Declaration of Michael Kinch relating to the nature of the biological deposit are included herewith.

Reconsideration and withdrawal of the rejection of claims 58-102 under 35 U.S.C. §112, first paragraph, is respectfully requested.

## Summary

It is respectfully submitted that the pending claims 58-102 are in condition for allowance and notification to that effect is respectfully requested.

If it is found that the claims are not in condition for allowance, Applicants request a second non-final Office Action, in order be assured of a full and fair opportunity to respond to the complete action on the merits as described in detail above.

The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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By: _____
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**APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS INCLUDING NOTATIONS TO INDICATE CHANGES MADE**
**Serial No.: 09/640,935**
**Docket No.: 290.0010 0101**

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted.

## In the Specification

The paragraph beginning at page 5, line 6, has been amended as follows:

EphA2 is expressed differently in normal and metastatic cells. In normal breast and prostate epithelial cells, EphA2 is enriched in within cites of cell adhesion. Conversely, in metastatic prostate cells EphA2 is diffusely distributed, and in metastatic breast cancer cells EphA2 is redistributed into the membrane ruffles. EphA2 expression is also known to be altered in lung and colon malignancies, and it is believed that EphA2 altered expression occurs in other types of [metastasis] metastases, particularly epithelial malignancies. Thus, techniques designed to alter EphA2 expression can be exploited to diagnose and treat metastatic disease.

The paragraph beginning at page 6, line 4, has been amended as follows:

Hybridomas producing antibodies specific to EphA2 have been selected. Use of the RIMMS technique has resulted in the production of a multiplicity of hybridomas producing monoclonal antibodies that specifically bind EphA2. To date, at least 450 hybridomas have been identified which produce antibodies capable of distinguishing malignant from normal cancer cells. Of the first four such hybridomas to be characterized, two recognize independent epitopes on EphA2. The first, D7, produces an antibody recognizing an intracellular epitope. The second, B2D6, produces an antibody that specifically binds an extracellular epitope of EphA2, a characteristic that enables its effective use for the diagnosis and treatment of selected metastatic tumors. Murine hybridomas B2D6 and D7 were deposited on December 8, 2000, with the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, and assigned ATCC Numbers PTA-2754 and PTA-2755, respectively.

The paragraph beginning at page 6, line 18, has been amended as follows:

It is known in the art to use antibodies to detect the presence or overexpression of a specific protein. Because EphA2 is overexpressed in metastatic cells, EphA2-specific antibodies of this invention may be used to detect this overexpression and, thus, to detect metastatic disease. Such techniques include but are not limited to western blotting, precipitation, agglutination, and ELISA assays. These techniques are well known in the art. Also, the extracellular epitope specificity of EphA2-specific antibodies of this invention can be exploited to detect changes in EphA2 localization which are associated with metastasis. In normal breast

and prostate epithelial cells, EphA2 is enriched in within cites of cell adhesion, whereas in metastatic cells, EphA2 distribution is altered. In metastatic prostate cells EphA2 is diffusely distributed, and in metastatic breast cancer cells EphA2 is redistributed into the membrane ruffles. EphA2 expression is also known to be altered in lung and colon malignancies, and it is believed that EphA2 altered expression occurs in other types of metastasis, particularly epithelial malignancies Techniques such as immunohistological staining or immunofluorescent microscopy are well known in the art and may be used to visualize EphA2 distribution. See, for example, U.S. Patent No. 5,514,554, hereby incorporated by reference. In order to detect overexpression or altered distribution of EphA2, the EphA2-specific antibodies may be labeled covalently or non-covalently with any of a number of known detectable labels, such as fluorescent or radioactive substances, as is known in the art. Alternatively, a secondary antibody specific for the antibodies of this invention is labeled with a known detectable label and used to detect the EphA2-specific antibodies in the above techniques. Thus, the antibodies of this invention provide methods to detect metastatic transformation.

The paragraph beginning at page 8, line 30, has been amended as follows:

Following the RIMMS strategy using tyrosine phosphorylated proteins from Ras-transformed human epithelial cells, hybridomas were screened, and an antibody specific for EphA2 has been isolated. This antibody, B2D6, was used to assess the levels of EphA2 expression in nontransformed prostatic epithelial cells and prostatic tumor cells. Low levels of EphA2 expression were found in non-transformed prostatic epithelial cells, but this EphA2 expression was enriched within sites of cell-cell contact and interacted with cell-bound ligand. Compared to non-transformed cells, two features distinguish EphA2 in metastatic prostate cancer cells: 1) EphA2 is overexpressed; 2) EphA2 is diffusely distributed and does not appear to interact with ligand. To confirm these data, western blots were performed using the EphA2 specific antibodies. EphA2 overexpression in human prostate cancer cells (LNCAP, DU145, PC3) directly correlates with their invasiveness *in vitro* and *in vivo*. Of the three lines tested, LNCAP is the least aggressive, DU145 is more aggressive, and PC3 is the most aggressive. As seen in Fig. 2, DU145 cells exhibit higher levels of EphA2 expression than LNCAP, and PC3 cells exhibit even higher levels of EphA2 expression. Similarly, as shown in Figs. 2B and 2C, EphA2 expression is elevated in variants of human prostatic epithelial cells transformed by oncogenic K-Ras or X-irradiation. The three lanes in Fig. 2B show "normal" MCL prostatic epithelial cells, and K-Ras and X-ray transformed cell lines derived therefrom. Similarly, the three lanes of Fig. 2C show "normal" 267B1 prostatic epithelial cells, and K-Ras and X-ray transformed cell lines derived therefrom. As seen in Figs. 2B and 2C, the transformed cells all exhibited elevated EphA2 levels. Fig. 3 shows similar western blots, except using prostate cancer cell lines from dogs. As shown in Fig. 3, consistent with the results from human cells, EphA2 is overexpressed in metastatic prostatic carcinoma cells derived from dogs with spontaneous prostate cancer.

The paragraph beginning at page 11, line 5, has been amended as follows:

It is believed that B2D6 decreases the growth of metastatic cells. Preliminary results reveal that B2D6 aggregates EphA2 and blocks about 50% of growth of metastatic breast cancer cells (which also overexpress EphA2) over the first four hours of incubation. Although EphA2 is not tyrosine phosphorylated in metastatic breast cancer cells, tyrosine phosphorylation is restored in these B2D6 treated cells. Thus, B2D6 is believed to restore normal EphA2 function.

The paragraph beginning at page 12, line 30, has been amended as follows:

The present EphA2 antibodies, particularly those produced by hybridoma B2D6, are effective in blocking the growth and invasiveness of prostate cancer cells *in vivo*. The efficacy of B2D6 in blocking the growth of primary prostate tumors using subcutaneous implantation of PC3 tumor cells in mice is determined by use of subcutaneous models. The primary advantages of subcutaneous models are the ease of implantation and subsequent monitoring of tumor size. $5x10^5$ PC3 cells are inoculated subcutaneously into the right craniolateral thorax (axilla) using aseptic technique. Tumors are measured every 3-4 days using vernier calipers until they reach a volume of 0.2-0.3 $cm^3$. At that time, the mice are divided into four groups (8-10 animals each): Group 1 (vehicle control), Groups 2-4 are treated with 0.1, 1.0, or 10 mg/kg B2D6, administered intraperitoneally, twice a week. The mice are then monitored every 3 days to measure tumor volume (with vernier calipers), body weight, and life span. After no greater than 60 days past implantation, the animals are sacrificed and postmortem evaluations of tumorigenesis, including measurement and weight of implanted tumors and proximal lymph nodes, macroscopic evaluation of soft tissues for tumors (lymph nodes and lung), and formalin fixation of the primary tumor and tissues, are performed. The tissues are evaluated by immunohistochemistry using D7 (another EphA2 specific antibody that is amenable to immunohistochemistry) to determine the level of EphA2 expression in the tumors. In particular, tumor cells that escape B2D6 treatment are studied to determine whether they have low levels of EphA2 expression. Also, EphA2 expression in the individual animals is correlated with tumor invasiveness.

The paragraph beginning at page 18, line 7, has been amended as follows:

To test if EphA2 could be stimulated by an agonist, $MCF^{EphA2}$ cells were suspended in soft agar in the presence or absence of 0.5 mg/mL EphrinA1-$F_c$. EphrinA1-$F_c$ increased the phosphotyrosine content of EphA2, and EphrinA1-$F_c$-treated cells exhibited reduced colony formation in soft agar by 49% relative to vehicle-treated controls ($P < 5x10^{-6}$). To test if EphA2 stimulation could alter cell behavior on Matrigel, the $MCF^{EphA2}$ cells were treated with 0.5 mg/mL EphrinA1-$F_c$, which restored a spherical phenotype that was comparable to non-transformed MCF-10A cells. Thus, EphA2 stimulation reverses the effects of EphA2

overexpression. [EphrinA1-$F_c$] Despite its inability to interact with its endogenous ligands, the EphA2 in $MCF^{EphA2}$ cells responded to exogenous stimuli.

## In the Claims

For convenience, all pending claims are shown below.

58. (Amended) A method for treatment of a patient having a metastatic tumor, said tumor comprising a population of metastatic cells that express EphA2, said method comprising administering to the patient a therapeutically effective amount of [an EphA2 agonist] a compound that increases the phosphotyrosine content of EphA2, wherein said administration reduces metastasis.

59. The method of claim 58 wherein the metastatic cells overexpress EphA2 as compared to normal cells.

60. The method of claim 58 wherein said administration inhibits proliferation of the metastatic cells.

61. The method of claim 58 wherein said administration reduces invasiveness of the metastatic cells compared to untreated metastatic cells.

62. (Amended) A method for treatment of a patient having a metastatic tumor, said tumor comprising a population of metastatic cells that express EphA2, said method comprising administering to the patient a therapeutically effective amount of [an EphA2 agonist] a compound that increases the phosphotyrosine content of EphA2, wherein said administration impedes proliferation of said metastatic cells.

63. The method of claim 62 wherein the metastatic cells overexpress EphA2 as compared to normal cells.

64. (Amended) A method for treatment of a patient having a metastatic tumor, said tumor comprising a population of metastatic cells that express EphA2, said method comprising administering to the patient a therapeutically effective amount of [an EphA2 agonist] a compound that increases the phosphotyrosine content of EphA2 in said metastatic cells as compared to untreated metastatic cells.

65. The method of claim 58 wherein the metastatic cells overexpress EphA2 as compared to normal cells.

66. (Amended) A method for reducing the invasiveness of a metastatic cancer cell that expresses EphA2, the method comprising contacting the metastatic cell with [an EphA2 agonist] a compound that increases the phosphotyrosine content of EphA2, thereby reducing the invasiveness of the metastatic cell compared to an untreated metastatic cell.

67. The method of claim 66 wherein the metastatic cell overexpresses EphA2 as compared to a normal cell.

68. The method of claim 66 wherein the metastatic cell is present in a mammalian patient.

69. (Amended) A method for reducing the proliferative behavior of a metastatic cancer cell that expresses EphA2, the method comprising contacting the metastatic cancer cell with [an EphA2 agonist] a compound that increases the phosphotyrosine content of EphA2, thereby reducing the proliferative behavior of said metastatic cell compared to an untreated metastatic cell.

70. The method of claim 69 wherein the metastatic cell overexpresses EphA2 as compared to a normal cell.

71. The method of claim 69 wherein the metastatic cell is present in a mammalian patient.

72. (Amended) A method for treatment of a patient having a metastatic tumor, said tumor comprising a population of metastatic cells that express EphA2, said method comprising administering to the patient a therapeutically effective amount of an [EphA2 agonistic] anti-EphA2 antibody that increases the phosphotyrosine content of EphA2, wherein said administration reduces metastasis.

73. The method of claim 72 wherein the metastatic cells overexpress EphA2 as compared to normal cells.

74. The method of claim 72 wherein said administration inhibits proliferation of the metastatic cells.

75. The method of claim 72 wherein said administration reduces invasiveness of the metastatic cells compared to untreated metastatic cells.

76. (Amended) The method of claim 72 wherein the [agonistic] anti-EphA2 antibody is a monoclonal antibody.

77. The method of claim 76 wherein the monoclonal antibody is humanized.

78. The method of claim 76 wherein the monoclonal antibody is conjugated to a cytotoxic agent.

79. (Amended) A method for treatment of a patient having a metastatic tumor, said tumor comprising a population of metastatic cells that express EphA2, said method comprising administering to the patient a therapeutically effective amount of an [EphA2 agonistic] anti-EphA2 antibody that increases the phosphotyrosine content of EphA2, wherein said administration impedes proliferation of said metastatic cells.

80. The method of claim 79 wherein the metastatic cells overexpress EphA2 as compared to normal cells.

81. (Amended) The method of claim 79 wherein the anti-EphA2 [agonistic] antibody is a monoclonal antibody.

82. The method of claim 81 wherein the monoclonal antibody is humanized.

83. The method of claim 81 wherein the monoclonal antibody is conjugated to a cytotoxic agent.

84. (Amended) A method for treatment of a patient having a metastatic tumor, said tumor comprising a population of metastatic cells that express EphA2, said method comprising administering to the patient a therapeutically effective amount of an anti-EphA2 [EphA2 agonistic] antibody that increases the phosphotyrosine content of EphA2 in said metastatic cells as compared to untreated metastatic cells.

85. The method of claim 84 wherein the metastatic cells overexpress EphA2 as compared to normal cells.

86. (Amended) The method of claim 84 wherein the anti-EphA2 [agonistic] antibody is a monoclonal antibody.

87. The method of claim 86 wherein the monoclonal antibody is humanized.

88. The method of claim 86 wherein the monoclonal antibody is conjugated to a cytotoxic agent.

89. (Amended) A method for reducing the invasiveness of a metastatic cancer cell that expresses EphA2, the method comprising contacting the metastatic cell with an anti-EphA2 [EphA2 agonistic] antibody that increases the phosphotyrosine content of EphA2, thereby reducing the invasiveness of the metastatic cell compared to an untreated metastatic cell.

90. The method of claim 89 wherein the metastatic cell overexpresses EphA2 as compared to a normal cell.

91. The method of claim 89 wherein the metastatic cell is present in a mammalian patient.

92. (Amended) The method of claim 89 wherein the anti-EphA2 [agonistic] antibody is a monoclonal antibody.

93. The method of claim 92 wherein the monoclonal antibody is humanized.

94. The method of claim 92 wherein the monoclonal antibody is conjugated to a cytotoxic agent.

95. (Amended) A method for reducing the proliferative behavior of a metastatic cancer cell that expresses EphA2, the method comprising contacting the metastatic cancer cell with an anti-EphA2 [EphA2 agonistic] that increases the phosphotyrosine content of EphA2,

thereby reducing the proliferative behavior of said metastatic cell compared to an untreated metastatic cell.

96. The method of claim 95 wherein the metastatic cell overexpresses EphA2 as compared to a normal cell.

97. The method of claim 95 wherein the metastatic cell is present in a mammalian patient.

98. (Amended) The method of claim 97 wherein the anti-EphA2 [agonistic] antibody is a monoclonal antibody.

99. The method of claim 97 wherein the monoclonal antibody is humanized.

100. The method of claim 97 wherein the monoclonal antibody is conjugated to a cytotoxic agent.

101. The method of any one of claims 58, 62, 64, 66 or 69 wherein the population of cells comprises cells selected from the group consisting of breast cancer cells, prostate cancer cells, lung cancer cells and colon cancer cells.

102. The method of any one of claims 72, 79, 84, 89 or 95 wherein the metastatic cancer cell is a cell selected from the group consisting of a breast cancer cell, prostate cancer cell, lung cancer cell and colon cancer cell.

PATENT
Docket No. 290.00100101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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|---|---|---|---|
| Applicant(s): | Michael S. Kinch et al. | Group Art Unit: | 3254 |
| Serial No.: | 09/640,935 | Examiner: | Misook Yu |
| Confirmation No.: | 3252 | | |
| Filed: | 17 August 2000 | | |

For: EPHA2 AS A THERAPEUTIC TARGET FOR METASTATIC CANCER
(As Amended)

#21
CD
3/7/03

DECLARATION OF MICHAEL S. KINCH UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Michael S. Kinch, Ph.D., declare and say as follows:

1. I am a co-inventor of the above-identified U.S. Patent Application Serial No. 09/640,935, filed August 17, 2000. I am currently employed as Associate Director of Oncology at MedImmune, Inc., located in Gaithersburg, Maryland. In 1993 I received my Ph.D. in Immunology from Duke University. From 1993-1996 I was a post-doctoral fellow at The University of North Carolina at Chapel Hill in Cancer Cell Biology. From 1996 to 2001 I was a Professor of Cellular Pharmacology at Purdue University, West Lafayette, Indiana, and an Adjunct Professor in the Department of Pharmacology at Indiana University School of Medicine, Indianapolis, Indiana. I joined MedImmune in 2001.

2. On information and belief, hybridoma B2D6 was produced by Katherine Kilpatrick, an employee of GlaxoWellcome, Inc., and delivered to me via FedEx in the course of my employment as a professor at Purdue University and prior to the filing date of the above-identified patent application. At the time it was delivered to me, hybridoma B2D6 was not isolated, characterized or identified as such, but was present in a bulk culture that contained several hybridoma cell lines.

3. I participated in or supervised the subcloning (isolation) of murine hybridoma cell line B2D6 from the bulk culture. Subcloning (isolation) was performed by Nicole Zantek, a graduate student in my laboratory at Purdue University. From the date of its isolation until the date of its deposit with the American Type Culture Collection (ATCC), I participated in or supervised the identification of, characterization of, maintenance of and recordkeeping associated with murine hybridoma cell line B2D6.

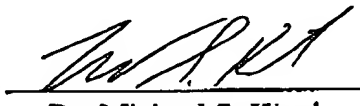
4. On or about December 1, 2000, I contacted Jane Stewart, a research associate under my direction at Purdue University, and instructed her to prepare samples of murine hybridoma cell line B2D6 for deposit with the ATCC. On information and belief, she thawed a frozen sample of the hybridoma B2D6 cell line and cultured additional samples of hybridoma cell line B2D6 required by the ATCC for deposit.

5. On December 7, 2000, Jane Stewart forwarded by Federal Express the murine hybridoma cell line B2D6 to the ATCC at 10801 University Blvd., Manassas, Virginia, 20110-2209, USA. The deposit is dated December 8, 2000. The cell line was viable at the time of deposit. Murine hybridoma cell line B2D6 has been assigned accession number ATCC No. PTA 2754. A copy of the Receipt from the ATCC regarding this deposit is attached to this statement as Exhibit A.

6. I confirm and corroborate that murine hybridoma cell line B2D6 from the same preparation as the sample deposited on December 8, 2000, with the ATCC and given ATCC Accession No. PTA 2754, produces a monoclonal antibody that specifically binds an extracellular epitope of the receptor tyrosine kinase EphA2, described in the specification of the above-identified application at, for example, page 6, lines 10-11 and claim 9 as originally filed.

7. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2-13-03
Date

By: 
Dr. Michael S. Kinch
Applicant

ATCC

10801 University Blvd • Manassas, VA 20110-2209 • Telephone: 703-365-2700 • FAX: 703-365-2745

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

*INTERNATIONAL FORM*

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

**To: (Name and Address of Depositor or Attorney)**

**Purdue University**
**Attn: Michael S. Kinch, Ph.D.**
**1246 Lynn Hall**
**West Lafayette, IN 47907-1246**



**Deposited on Behalf of:** Purdue University

**Identification Reference by Depositor:**
Murine Hybridoma: B2D6
(Ref: Docket or Case No.: P-98086-00-US)

**Patent Deposit Designation**
PTA-2754

The deposits were accompanied by: __ a scientific description _ a proposed taxonomic description indicated above. The deposits were received December 8, 2000 by this International Depository Authority and have been accepted.

**AT YOUR REQUEST:** X We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested December 12, 2000. On that date, the cultures were viable.

**International Depository Authority:** American Type Culture Collection, Manassas, VA 20110-2209 USA.

**Signature of person having authority to represent ATCC:**

Tanya Nunnally, Patent Specialist, Patent Depository

**Date:** February 7, 2001

cc: Victoria Sandberg

PATENT
Docket No. 290.0010 0101

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| Applicant(s): | Michael S. Kinch et al. | Group Art Unit: | 3254 |
| Serial No.: | 09/640,935 | Examiner: | Misook Yu |
| Confirmation No.: | 3252 | | |
| Filed: | 17 August 2000 | | |

For: EPHA2 AS A THERAPEUTIC TARGET FOR METASTATIC CANCER (As Amended)

## STATEMENT OF AVAILABILITY

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

1. I am an attorney of record in the above-entitled application.

2. Hybridoma cell line B2D6, referred to at page 6, lines 10-11, was deposited and is available from the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA, 20110-2209, USA, on December 8, 2000, in accordance with the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure, as evidenced by the attached copies of the Deposit Receipt.

3. Hybridoma cell line B2D6 was identified as "murine hybridoma B2D6," was assigned ATCC number PTA 2754.

4. Upon issuance of a patent out of the above-identified application, all restrictions, subject to the provisions of 37 C.F.R. 1.808(b), upon the availability of hybridoma cell line B2D6 to the public will be irrevocably removed, and the deposits will be replaced if viable samples cannot be dispensed by the depository.

CERTIFICATE UNDER 37 C.F.R. 1.10:

The undersigned hereby certifies that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated below and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Jacquelyn K. Torbert
JACQUELYN K. TORBERT
"Express Mail" mailing label number: EV153782125US
Date of Deposit: 13 February 2003

13 February 2003
Date

Respectfully submitted for

Purdue Research Foundation

By
Mueting, Raasch & Gebhardt, P.A.
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Minneapolis, MN 55458-1415
Phone: (612)305-1220
Facsimile: (612)305-1228
**Customer Number 26813**

26813
PATENT TRADEMARK OFFICE

By: _____
Victoria A. Sandberg
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PATENT
Docket No. 290.0010 0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Applicant(s): | Kinch et al. | Group Art Unit: | 1642 |
| Serial No.: | 09/640,935 | Examiner: | M. Yu |
| Confirmation No.: | 3254 | | |
| Filed: | 17 August 2000 | | |

For: EPHA2 AS A THERAPEUTIC TARGET FOR METASTATIC CANCER
(As Amended)

**REQUEST TO CORRECT INVENTORSHIP PURSUANT TO §1.48(b)**

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants respectfully request that the above-identified patent application be amended in accordance with 37 C.F.R. §1.48(b) to delete Katherine E. Kilpatrick as a named inventor.

REMARKS

The following individuals were named inventors of the above-identified patent application according to a Declaration and Power of Attorney submitted February 14, 2001: Michael S. Kinch, Nicole D. Zantek, Katherine E. Kilpatrick and Patrick W. Hein.

It is respectfully submitted that prosecution of the above-identified patent application has resulted in an election of claims, pursuant to the Restriction Requirement mailed May 6, 2002, such that fewer than all of the currently named inventors are the inventors of the invention presently claimed herein. Specifically, only Michael S. Kinch, Nicole D. Zantek and/or Patrick W. Hein are inventors of the subject matter of pending claims 58-102; Katherine E. Kilpatrick is not an inventor of said subject matter. It is therefore respectfully requested that Katherine E. Kilpatrick be deleted as an inventor in the above-identified patent application.

Please charge Deposit Account 13-4895 in the amount of $130.00 for the correction of inventorship, in accordance with 37 C.F.R. §§1.48(b)(2) and 1.17(i). In addition, please charge any additional fees required for this petition to Deposit Account No. 13-4895.

**Request to Correct Invent rship Pursuant to §1.48(b)**
Applicant(s): Michael S. Kinch et al.
Serial No.: 09/640,935
Confirmation No.: 3254
Filed: 17 August 2000
For: EPHA2 AS A THERAPEUTIC TARGET FOR METASTATIC CANCER (As Amended)

If a telephone conference would be of assistance, please contact the below-signed attorney at (612)305-1226.

CERTIFICATE UNDER 37 C.F.R. 1.10:

The undersigned hereby certifies that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated below and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Jacquelyn K. Torborg
JACQUELYN K. TORBORG

"Express Mail" number: EV153782125US
Mailed: 13 February 2003

13 February 2003
Date

Respectfully submitted for

Michael S. Kinch et al.

By
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